Translocation (X;6) in a female with Duchenne muscular dystrophy: implications for the localisation of the DMD locus

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SUMMARY   A female with Duchenne muscular dystrophy who was a carrier of a balanced translocation t(X;6)(p21;q21) is reported. Four other previously described (X;A) translocations associated with DMD share with the present case a breakpoint at Xp21. The extremely low probability of five independent (X;A) translocations having a breakpoint at Xp21 points to a non-random association of this site with the DMD phenotype. A DMD locus at Xp21 could be damaged by the translocation, giving rise to Duchenne muscular dystrophy. Alternatively, a pre-existing DMD gene could weaken the chromosome, favouring breaks at Xp21.

Duchenne muscular dystrophy (DMD) is a severe X linked condition characterised by a progressive degeneration of skeletal muscles. Mild clinical symptoms have been reported in female carriers of the DMD gene with normal karyotypes.[1-4] According to Emery[5] this occurs in approximately 8% of heterozygous women and the degree of manifestation ranges from pseudohypertrophy of the calf muscles to marked proximal muscle wasting and weakness. Such manifestations can be explained on the basis of preferential inactivation of the X chromosome bearing the normal allele.

A number of pedigrees have been reported with a type of Duchenne muscular dystrophy affecting both girls and boys and having an apparent autosomal recessive mode of inheritance.[6-8] This form differs from the typical X linked DMD because it is less severe, the onset is usually between 5 and 14 years of age, and the progression is slower. Serum enzymes are raised but not usually in the same range as in X linked DMD.

DMD with a clinical course as severe as the one in affected boys has been reported in females with an XO sex chromosomal constitution in a large proportion of cells[9-11] or with a structurally abnormal X chromosome.[12]

More recently, four independent reports have described typical DMD in female carriers of X; autosome translocations.[13-16] Although different

autosomes were involved, it seems that the breakpoints on the X chromosome affected the same band in the four cases, suggesting that a locus for DMD might be located at this site.[16]

We report here an additional case of DMD in a female carrier of an apparently balanced translocation t(X;6)(p21;q21). The possible localisation of the DMD locus is discussed.

Case report

The proband (fig 1) with DMD is an 11½-year old girl born to unrelated and healthy parents. The mother was 29 and the father 26 at the time of her birth. She is an isolated case in the family and has five normal maternal uncles. Her mother had a total of three children (two boys and the proband) from three different husbands. The patient is the second child and neither her older nor younger half-brothers, aged 22 and 5, is affected.

She was born at term with a birthweight of 3700 g and a length of 50 cm. According to her mother, her physical and motor development was normal until the age of 5, when she began to fall down frequently and to have difficulty in running and climbing stairs. After that her physical disability progressed steadily and she was confined to a wheelchair at the age of 10. She is now unable to walk or stand without support.
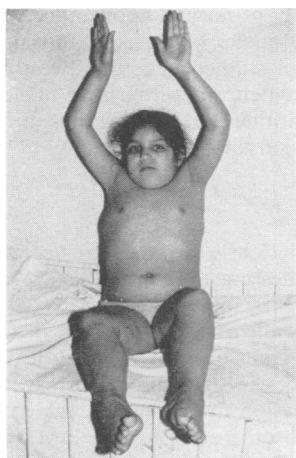
Clinical examination at 11½ years revealed the

FIG 1 *Proband at 11½ years old.*

following features: height of 127 cm (below the 3rd centile), span of 123 cm, and weight of 36 kg (well above the 3rd centile for her height). Her external genitalia were normal and she was premenarchal. She did not have any breast development or axillary hair, but had incipient pubic hair.

Neurological examination showed generalised proximal weakness and symmetrical wasting which was more pronounced in the quadriceps, gluteus, and iliopsoas muscles. In the upper limbs the pectorals, intercostal, and biceps muscles were already involved. Muscular hypertrophy was present in the calves. The tendon reflexes in the upper limbs were diminished and the knee jerks were absent, whereas the ankle jerks were preserved bilaterally. Deep and superficial sensibility was preserved.

Psychological evaluation revealed apparently normal intellectual performance considering her home environment.

The patient's father and older half-brother were not available for study.

ELECTROMYOGRAPHY
This showed a pattern characteristic of myopathy with polyphasic motor unit action potentials of low amplitude and short duration. There were no signs of denervation and there was normal nerve conduction velocity.

MUSCLE BIOPSY
There was marked variation in fibre size, rounded opaque fibres with internal nuclei, and degeneration and proliferation of connective and adipose tissues.

ELECTROCARDIOGRAM
She had sinusal tachychardia.

SERUM ENZYMES
Serum creatine kinase (CK) activity was measured in Sigma units (normal is up to 10 for adult females and up to 20 for young children) and pyruvate-kinase (PK) as μmol/ml/h (normal is up to 2·5 for adult females and 7·0 for young children). The results for CK and PK in the proband, her mother, and younger half-brother were, respectively, 247·0 SU and 28·1 μmol/ml/h; 8·0 SU and 2·38 μmol/ml/h; 15·5 SU and 6·4 μmol/ml/h. For the proband and her mother the above values represent the mean of three independent determinations.

ESTIMATION OF HETEROZYGOSITY RISKS
The probability that our patient's mother is a carrier of the Duchenne gene was estimated as p=0·06, based on genetic analysis of the pedigree and serum CK and PK activities, according to the method described in Zatz and Otto.[17]

GENETIC MARKERS
No abnormalities were observed with regard to colour vision or G6PD in the proband, her mother, or half-brother. Xg blood groups were performed by Dr Ruth Sanger at the MRC Blood Group Unit in London. The mother was found to be Xg(a+) while both the patient and her half-brother were Xg(a—).

KARYOTYPE ANALYSIS
Chromosome studies were performed on cultured lymphocytes and fibroblasts from a skin biopsy of the proband and on cultured lymphocytes of her mother and half-brother. Trypsin G banding was performed according to Seabright.[18] Late replication patterns of the X chromosome were studied after incorporation of 5-BrdU and Giemsa staining (Zakharov and Egolina,[19] modified).

The patient was found to be a carrier of a balanced translocation between the long arm of a chromosome 6 and the short arm of an X (fig 2). On the translocated X, the band corresponding to p21 was reduced to approximately half its normal length. This led us to put the breakpoint at the middle of

FIG 2 *Trypsin-Giemsa banded chromosomes X, der (X), 6, and der (6) of the patient.*

Xp21. On the translocated 6, the band corresponding to q22 was represented by a thinner band, interpreted as part of Xp21. Since on the der(X) the positive bands Xp21 and 6q22 appeared to be separated by a thin negative band, it was concluded that a small part of 6q21 had also been translocated. The breakpoint was, therefore, located at 6q21 (fig 3).

Among 56 informative lymphocytes after 5-BrdU incorporation, the normal X was late replicating in 55 (fig 4). In one cell, the long arm of the translocated X was the only despiralised segment.
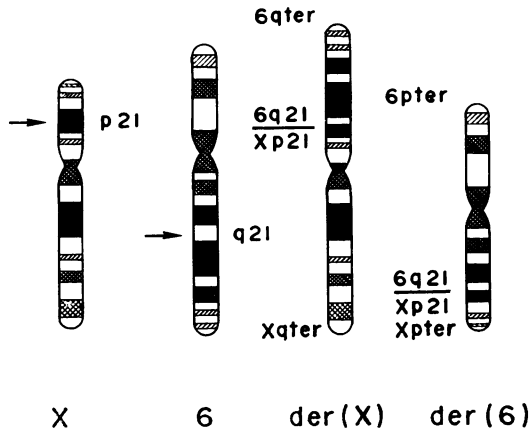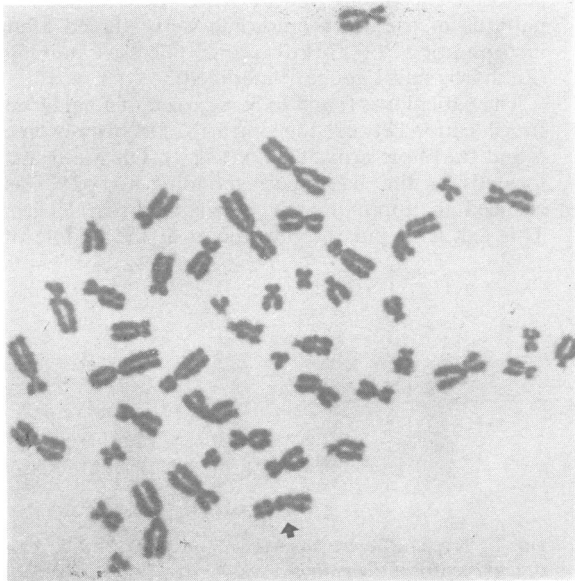

6qter

6q21
Xp21

6pter

p21

q21

6q21
Xqter

6q21
Xp21
Xpter

X   6   der(X)   der(6)

FIG 3   *Diagram of the rearrangement t(X;6)(Xqter →*
Xp21 :: 6q21 → 6qter;6pter → 6q21 :: Xp21 → Xpter).
Based on Yunis et al.[68]

A Barr body of normal appearance was observed in 36 of 200 nuclei in a buccal smear. A normal female control studied in a blind test at the same time showed 34 chromatin positive nuclei.

Both the mother and half-brother of the proband have normal karyotypes.

Discussion

Our proband clearly belongs to the rare group of females manifesting the whole picture of X linked DMD and carrying a structurally abnormal X. This is the result of the expression of the recessive gene on the translocation X and the non-random inactivation of the structurally normal X.

A translocation involving a break at any site of an X chromosome carrying the DMD gene would lead to the DMD phenotype. The fact that the breakpoint occurred at Xp21 in all five X;autosome translocations in females with DMD leads us to question the independence of these two events.

THE NON-RANDOMNESS OF THE TWO EVENTS
The table shows the frequencies of the breakpoints on the X, which were determined by banding methods, in published (X;A) translocations. Those ascertained through DMD female patients were not included. Among the breaks, three (0·060) were located at Xp21 and this does not differ from the expected frequency (0·059) if the number of breaks is proportional to the length of the band. Therefore, Xp21 cannot be considered as a 'hot point'. The probability of five translocations (X;A) having a

FIG 4   *Metaphase after 5-BrdU incorporation. Arrow points to the normal late replicating X.*

TABLE   *Breakpoints in X;autosome translocations*

Breakpoint on X	No of translocations	Breakpoint on X	No of translocations
p22	7 [20-26]	q21	7 [28] [44-48]
p21	3 [21] [27] [28]	q22	3 [49-51]
p11	9 [26] [28-35]	q24	1 [52]
q11	2 [36] [37]	q26	4 [53-56]
q12	4 [22] [38-40]	q27	3 [57-59]
q13	3 [41-43]	q28	4 [39] [60-62]

breakpoint at Xp21 can be estimated as $(0.060)^5 = 7.8 \times 10^{-7}$. This figure points to a non-random association of the breakpoints at Xp21 with the DMD phenotype.

The fact that three other translocations with breakpoints at Xp21 have been described[21] [27] [28] in patients with no apparent signs of DMD does not invalidate the non-random association, since the breaks could have occurred at sites other than that in the DMD patients.

Moreover, if an association does not exist, the number of cases of female carriers of (X;A) translocations with the DMD phenotype would be much smaller than the number of patients with Turner syndrome with DMD, since XO females occur much more frequently and are more easily ascertained than females with (X;A) translocations. Yet, apparently, only three cases of patients with X aneuploidies and DMD have been reported.[9-11]

Either of the two following hypotheses would explain the non-random association of an (X;A) translocation with the DMD phenotype in a female. (1) A DMD locus (either structural or regulatory) at Xp21 would be damaged by the translocation giving rise to DMD. (2) A pre-existing DMD gene at Xp21 would weaken the chromosome, favouring breaks at this site.

THE FIRST HYPOTHESIS

According to the first hypothesis a subject with the translocation which causes the DMD gene to appear would be affected by DMD and would not reproduce, and the gene could not be transmitted by a mother with a normal karyotype if the gene originates from a translocation. Therefore, the hypothesis requires that both events occur de novo.

In the other four females with DMD who carried a balanced (X;A) translocation, the de novo occurrence of the rearrangement has been demonstrated. In the present case, it was not possible to exclude the possibility entirely that the translocation had been paternally inherited from the proband's father, since he was not available for examination. However, it seems to be the rule that male carriers of a balanced (X;A) translocation are infertile.[44] This favours the hypothesis that the translocation carried by our proband also occurred de novo.

With respect to the origin of the DMD gene, all five patients are isolated cases. Both CK and PK levels in the mother of our proband were within the normal range and these results, when combined with data from the pedigree, gave an estimated low probability (0.06) of her being a heterozygote. Repeated CK determinations in the family described by Greenstein *et al*[13] suggested that that patient's mother was not a DMD carrier. Likewise, in the case studied by Lindenbaum *et al*[16] pedigree analysis combined with CK testing showed it to be unlikely that the patient's mother was a heterozygote for DMD (p=0.01). On the other hand, Verellen *et al*[14] stated that the mother of their patient was a carrier, based on "elevated serum enzymes and myopathic electromyogram". Serum CK determinations and EMG led Canki *et al*[15] also to favour the possibility of the mother being heterozygous. However, in these two latter reports no results were given for serum enzymes or electromyogram patterns and no reference was made to the method used for estimating the probability of the mother being a carrier. Thus, we cannot discard the possibility that the gene might not have been inherited in these cases either.

THE SECOND HYPOTHESIS

The second hypothesis requires, like the first one, the de novo occurrence of the translocation, but not that of the DMD gene. A heterozygous mother could transmit the DMD gene to a daughter in whom the translocation could occur. Therefore, the demonstration that a mother with a daughter with a translocation and the DMD phenotype is indeed a heterozygote would favour the second hypothesis. This would be the case if the mothers of the patients of Verellen *et al*[14] and Canki *et al*[15] were shown to be heterozygotes. This hypothesis would be confirmed if some of the affected females with a translocation had affected male relatives.

LINKAGE DATA

Family studies have shown no evidence of linkage between the DMD locus and either Xg or the colour blindness/G6PD cluster.[63] The closest estimate is that the Xg locus is located on the terminal portion of the X chromosome short arm[64] and the G6PD/colour blindness cluster on the terminal segment of the long arm, Xq26→Xqter.[65] Therefore, the DMD locus is excluded from both extremities of the X chromosome.

According to Race and Sanger,[64] the limit of measurable X linkage from human data likely to be collected is about 30 centimorgans. On the other hand, the estimated length of the X chromosome in terms of cross-over units is 200 to 250 centimorgans.[66] [67] Since the segment Xp21→Xpter

corresponds to 20% of the length of the chromosome, it corresponds to 40 to 50 centimorgans. Therefore the DMD locus could well be located at Xp21 and show no measurable linkage with the Xg locus.

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